PCT/US2005/009996

WHAT IS CLAIMED IS:

1. A method of treating a condition responsive to inhibition of 11β-hydroxysteroid dehydrogenase-1 in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of structural formula I:

or a pharmaceutically acceptable salt thereof; wherein

each n is 0, 1, or 2;

each p is 0, 1, or 2;

R1 is aryl or heteroaryl wherein heteroaryl is selected from the group consisting of

pyridyl,

thienyl,

furyl,

pyrazolyl,

thiazolyl,

oxazolyl,

imidazolyl,

indolyl,

benzothiophenyl,

benzofuryl, and

benzimidazolyl;

in which aryl and heteroaryl are substituted with one to four substituents independently selected from R^3 , R^4 , and R^5 ;

R² is selected from the group consisting of

C₁₋₄ alkyl,

C₂₋₄ alkenyl, and

(CH₂)_n-C₃₋₆ cycloalkyl;

 $R^3,\,R^4,\,$ and R^5 are each independently selected from the group consisting of

hydrogen,

formyl,

C₁₋₆ alkyl,

```
C<sub>2-6</sub> alkenyl,
(CH<sub>2</sub>)<sub>n</sub>-aryl,
(CH<sub>2</sub>)<sub>n</sub>-heteroaryl,
(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl,
(CH<sub>2</sub>)<sub>n</sub>C<sub>3</sub>-7 cycloalkyl,
halogen,
or7,
(CH_2)_nN(R^7)_2,
cyano,
(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>7</sup>,
NO_2,
(CH_2)_nNR^7SO_2R^6,
(CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>,
(CH_2)_nS(O)_pR^6,
(CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>OR<sup>7</sup>,
(CH<sub>2</sub>)<sub>n</sub>NR<sup>7</sup>C(O)N(R<sup>7</sup>)<sub>2</sub>,
(CH_2)_n C(O) N(R^7)_2,
(CH_2)_nNR^6C(O)R^6,
(CH<sub>2</sub>)<sub>n</sub>NR<sup>6</sup>CO<sub>2</sub>R<sup>7</sup>,
O(CH_2)_nC(O)N(R^7)_2,
CF<sub>3</sub>,
CH2CF3,
OCF<sub>3</sub>,
OCHCF2, and
OCH2CF3;
```

wherein aryl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkyl, trifluoromethyl, trifluoromethoxy, and C_{1-4} alkoxy; and wherein any methylene (CH₂) carbon atom in R^3 , R^4 , and R^5 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH₂) carbon atom are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each ${\rm R}^6$ is independently selected from the group consisting of

```
C<sub>1-8</sub> alkyl,
C<sub>2-4</sub> alkynyl,
(CH<sub>2</sub>)<sub>n</sub>-aryl,
```

(CH₂)_n-heteroaryl, and

(CH₂)_nC₃-7 cycloalkyl;

wherein alkyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, oxo, C_{1-4} alkoxy, C_{1-4} alkylthio, hydroxy, and amino; and aryl and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from cyano, halogen, hydroxy, amino, carboxy, trifluoromethyl, trifluoromethoxy, C_{1-4} alkyl, and C_{1-4} alkoxy; or two R^6 groups together with the atom to which they are attached form a 5- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₀₋₄ alkyl; and each R^7 is hydrogen or R^6 .

- 2. The method of Claim 1 wherein said condition is selected from the group consisting of diabetes, obesity, insulin resistance, a lipid disorder, hypertension, atherosclerosis, and Metabolic Syndrome.
 - 3. The method of Claim 1 wherein R² is methyl.
- 4. The method of Claim 1 wherein R³ is hydrogen and R⁴ and R⁵ are each independently selected from the group consisting of amino, halogen, hydroxy, nitro, trifluoromethyl, trifluoromethoxy, difluoromethoxy, C₂₋₃ alkynyloxy, C₁₋₅ alkyl, cyclopropyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, and C₁₋₄ alkylsulfonyl.
- 5. The method of Claim 1 wherein R¹ is phenyl or naphthyl each of which is substituted with one to three substituents independently selected from R³.
- 6. The method of Claim 5 wherein R³ is selected from the group consisting of amino, halogen, hydroxy, nitro, trifluoromethyl, trifluoromethoxy, difluoromethoxy, C₁₋₅ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylsulfonyl, phenyl, phenyloxy, phenylthio, and phenylsulfonyl, wherein the phenyl moiety of each is unsubstituted or substituted with one to three substituents independently selected from cyano, halogen, hydroxy, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkyl, and C₁₋₄ alkoxy.
 - 7. The method of Claim 6 wherein R² is methyl.

8. The method of Claim 1 wherein R¹ is heteroaryl substituted with one to three substituents independently selected from R³.

- 9. The method of Claim 8 wherein R² is methyl.
- 10. The method of Claim 8 wherein heteroaryl is pyrazolyl or indolyl, each of which is substituted with one to three substituents independently selected from R³.
 - 11. The method of Claim 10 wherein R² is methyl.
- 12. The method of Claim 10 wherein R³ is selected from the group consisting of amino, halogen, hydroxy, nitro, trifluoromethyl, trifluoromethoxy, difluoromethoxy, C₁₋₅ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylsulfonyl, phenyl, phenyloxy, phenylthio, and phenylsulfonyl, wherein the phenyl moiety of each is unsubstituted or substituted with one to three substituents independently selected from cyano, halogen, hydroxy, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkyl, and C₁₋₄ alkoxy.
 - 13. The method of Claim 12 wherein R² is methyl.
- 14. The method of Claim 1 wherein the compound of structural formula I is selected from the group consisting of:

or a pharmaceutically acceptable salt thereof.

- 15. The method of Claim 2 wherein said diabetes is Type 2 diabetes.
- 16. A compound of structural formula II:

or a pharmaceutically acceptable salt thereof; wherein

each n is 0, 1, or 2;

each p is 0, 1, or 2;

 $R^{\mbox{\it 8}}$ is naphthyl or heteroaryl wherein heteroaryl is selected from the group consisting of

pyridyl,

thienyl,

furyl,

pyrazolyl,

```
thiazolyl,
            oxazolyl,
            imidazolyl,
            indolyl,
            benzothiophenyl,
            benzofuryl, and
            benzimidazolyl;
in which naphthyl and heteroaryl are substituted with one to three substituents independently selected
from R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup>;
R<sup>2</sup> is methyl or cyclopropyl;
R3, R4, and R5 are each independently selected from the group consisting of
           hydrogen,
            formyl,
            C<sub>1-6</sub> alkyl,
            C2-6 alkenyl,
            (CH<sub>2</sub>)<sub>n</sub>-aryl,
           (CH<sub>2</sub>)<sub>n</sub>-heteroaryl,
           (CH<sub>2</sub>)<sub>n</sub>-heterocyclyl,
           (CH<sub>2</sub>)<sub>n</sub>C<sub>3</sub>-7 cycloalkyl,
           halogen,
           OR7,
           (CH_2)_nN(R^7)_2,
           cyano,
           (CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>7</sup>,
           NO<sub>2</sub>,
           (CH_2)_nNR^7SO_2R^6,
           (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>,
           (CH_2)_nS(O)_pR^6,
           (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>OR<sup>7</sup>,
           (CH_2)_nNR^7C(O)N(R^7)_2,
           (CH_2)_n C(O) N(R^7)_2,
           (CH_2)_nNR^6C(O)R^6,
           (CH<sub>2</sub>)<sub>n</sub>NR<sup>6</sup>CO<sub>2</sub>R<sup>7</sup>,
           O(CH_2)_nC(O)N(R^7)_2,
           CF3,
```

PCT/US2005/009996

CH₂CF₃,

OCF₃,

OCHCF2, and

OCH2CF3;

wherein aryl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄ alkyl, trifluoromethyl, trifluoromethoxy, and C₁₋₄ alkoxy; and wherein any methylene (CH₂) carbon atom in R³, R⁴, and R⁵ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl; or two substituents when on the same methylene (CH₂) carbon atom are taken together with the carbon atom to which they are attached to form a cyclopropyl group; each R⁶ is independently selected from the group consisting of

C₁₋₈ alkyl,

(CH₂)_n-aryl,

(CH2)n-heteroaryl, and

(CH₂)_nC₃-7 cycloalkyl;

wherein alkyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, oxo, C₁₋₄ alkoxy, C₁₋₄ alkylthio, hydroxy, amino; and aryl and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from cyano, halogen, hydroxy, amino, carboxy, trifluoromethyl, trifluoromethoxy, C₁₋₄ alkyl, and C₁₋₄ alkoxy; or two R⁶ groups together with the atom to which they are attached form a 5- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄ alkyl; and each R⁷ is hydrogen or R⁶.

- 17. The compound of Claim 16 wherein R² is methyl.
- 18. The compound of Claim 16 wherein R⁸ is indolyl or pyrazolyl substituted with one to three substituents independently selected from R³.
 - 19. The compound of Claim 18 wherein R² is methyl.
 - 20. A compound which is selected from the group consisting of:

4-methyl-3,5-bis[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole; 4-methyl-3-[4-(methylthio)-2-(trifluoromethyl)phenyl]-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole;

```
4-methyl-3-(4-pentylphenyl)-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(2-chlorophenyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(1-methoxy-2-naphthyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
4-[5-(2-\text{chlorophenyl})-4-\text{methyl}-4H-1,2,4-\text{triazol}-3-yl}-1-\text{methyl}-1H-\text{indole};
4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}-1-methyl-1H-indole;
3-(2-bromophenyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(7-chloro-1-methoxy-2-naphthyl)-4-methyl-5-[2-(trifluoromethyl)-4H-1,2,4-triazole;
4-[4-methyl-5-(1-methyl-1H-indol-4-yl)-4H-1,2,4-triazol-3-yl]phenol;
3-(2,4-dichlorophenyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-[2,4-bis(trifluoromethyl)phenyl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(2-chlorophenyl)-5-(2,4-dichlorophenyl)-4-methyl-4H-1,2,4-triazole;
3-(2-chloro-4-fluorophenyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(2,4-dichlorophenyl)-4-methyl-5-[2-(methylthio)phenyl]-4H-1,2,4-triazole;
3-(2,4-dichlorophenyl)-4-methyl-5-(2-methylphenyl)-4H-1,2,4-triazole;
3-(2-chlorophenyl)-5-[5-(2-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]-4-methyl-4H-1,2,4-triazole;
4-[5-(2-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl]-1-methyl-1H-indole;
4-methyl-3-(2-methyl-1-naphthyl)-5-[2-(trifluoromethyl)phenyl]-4-methyl-4H-1,2,4-triazole;
3-(1,4-dichloro-2-naphthyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(4-chloro-1-methoxy-2-naphthyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(1-fluoro-2-naphthyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
N-methyl-2-{4-methyl-5-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}naphthalen-1-amine;
3,5-bis-(2,4-dimethylphenyl)-4-methyl-4H-1,2,4-triazole;
3-(2,4-dichlorophenyl)-5-[2-(ethylthio)phenyl]-4-methyl-4H-1,2,4-triazole;
3-(2-cyclopropylphenyl)-5-(2,4-dichlorophenyl)-4-methyl-4H-1,2,4-triazole;
3-[(2-chloro-4-(ethylthio)phenyl)]-5-(2-fluorophenyl)-4-methyl-4H-1,2,4-triazole;
3-(2-methoxyphenyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(2,6-dichlorophenyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-(2-chlorophenyl)-5-[(2-difluoromethoxy)phenyl]-4-methyl-4H-1,2,4-triazole;
3-(2-chloro-4-fluorophenyl)-5-(2-chlorophenyl)-4-methyl-4H-1,2,4-triazole;
3-(2,4-dichlorophenyl)-5-[(2-difluoromethoxy)phenyl]-4-methyl-4H-1,2,4-triazole;
4-methyl-3-(2-phenoxyphenyl)-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
4-methyl-3-[2-(trifluoromethoxy)phenyl]-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
4-methyl-3-[2-(prop-2-yn-1-yloxy)phenyl]-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-{2-[(4-chlorophenyl)thio]phenyl}-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
3-[2-(difluoromethoxy)phenyl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole;
```

PCT/US2005/009996

3-(2-ethoxyphenyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 4-methyl-3-(2-propoxyphenyl)-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3,5-bis(2-chlorophenyl)-4-methyl-4H-1,2,4-triazole; 3,5-bis(2,3-dichlorophenyl)-4-methyl-4H-1,2,4-triazole; 3-(3-chloro-2-naphthyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-(5-chloro-6-methoxy-1-naphthyl)-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-[2-(4-chlorophenoxy)phenyl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-[4-(4-chlorophenoxy)phenyl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-[4-chloro-5-(2-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole: 4-methyl-3-(2,4,6-trichloro-1-naphthyl)-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-(2-chlorophenyl)-4-methyl-5-[2-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 3-(2-bromophenyl)-5-(2-methoxyphenyl)-4-methyl-4H-1,2,4-triazole; 3-(2,3-dichlorophenyl)-4-methyl-5-(2-methylphenyl)-4H-1,2,4-triazole; 3-(2,3-dichlorophenyl)-5-(2-methoxyphenyl)-4-methyl-4H-1,2,4-triazole; 3-(2-bromophenyl)-4-methyl-5-(2-methylphenyl)-4H-1,2,4-triazole; 4-methyl-3-(2-methylphenyl)-5-[2-(trifluoromethoxyl)phenyl]-4H-1,2,4-triazole; 3-(2-chlorophenyl)-4-cyclopropyl-5-[(2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-(4-chloro-3-methoxy-2-naphthyl)-4-methyl-5-[(2-(methylthio)phenyl]-4H-1,2,4-triazole; 3-[2-(4-chlorophenoxy)phenyl]-4-methyl-5-[(2-(methylthio)phenyl]-4H-1,2,4-triazole; 3-[2-(4-chlorophenoxy)phenyl]-4-methyl-5-[(2-(methylsulfonyl)phenyl]-4H-1,2,4-triazole; 3-(2-chlorophenyl)-5-(2,3-dichlorophenyl)-4-methyl-4*H*-1,2,4-triazole; 3-(2-bromophenyl)-5-(2-chlorophenyl)-4-methyl-4*H*-1,2,4-triazole;

21. A pharmaceutical composition comprising a compound in accordance with Claim 16 in combination with a pharmaceutically acceptable carrier.

3-[2-(4-fluorophenoxy)phenyl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole; 3-(2-chlorophenyl)-5-[2-chloro-3-(trifluoromethyl)phenyl]-4-methyl-4*H*-1,2,4-triazole; and

4-[4-methyl-5-(1,2,3-trimethyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl]phenol;

or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound in accordance with Claim 20 in combination with a pharmaceutically acceptable carrier.